REMARKS

Claims 1-8 are pending.

Rejections Under 35 U.S.C. § 103(a)

Claims 1-8 are rejected under 35 U.S.C. § 103(a) as unpatentable over Schinazi *et al.* (U.S. Patent No. 5,703,058) and Thyagarajan (U.S. Patent No. 6,589,570). Specifically, the Examiner contends that Schinazi *et al.* teaches that "FTC exhibits antiviral activity against HBV," that "alpha-interferon is effective for HBV," "that L(-)FMAU is an example of antiviral agent that can be used in combination with (-)enantiomer of FTC for the treatment of HBV infections," and that "[o]ne of ordinary skill in the art would have recognized that the results of the combination were predictable" (page 3 of the Office Action). The Examiner contends that Thyagarajan describes certain agents that "are successful in the treatment of HBV infection are *inter alia* interferons such as Alpha interferon, Beta interferon and Gamma interferon" (Table 1 col. 2).

Applicants strongly disagree with this rejection. The pending claims recite a method for the treatment or prophylaxis of a human infected with HBV comprising administering in combination or alternation an effective amount of: β-2-hydroxymethyl-5-(5-fluorocytosin-1-yl)-1,3-oxathiolane (β-L-FTC); 1-(2'-deoxy-2'-fluoro-β-L-arabinofuranosyl)-thymine (L-FMAU); and interferon; or their pharmaceutically acceptable salts, independently optionally in pharmaceutically acceptable carriers. The claimed method provides several unforeseen advantages for the treatment of hosts infected with HBV.

The specification describes the evaluation of L-FMAU, β-L-FTC and Ad-interferon in treating HBV infections in *in vivo* experiments using the woodchuck model of HBV infection (see Examples 1-7). This treatment induced remarkably rapid reduction of the viral load (average of 5 log10 decrease within two weeks), which is significant compared to results obtained with β-L-FTC or L-FMAU alone. The results showed a significant inhibition of viremia of all animals treated with L-FMAU, β-L-FTC and Ad-interferon. Viremia decreased to undetectable levels in less than two weeks after the beginning of therapy and remained

suppressed for a several months following withdrawal of treatment. Overall, the viral load in all treated animals did not return to pretreatment levels.

Furthermore, a marked decrease in intrahepatic replicative intermediates of viral DNA (82-93% decrease compared to the pretreatment levels) was observed in animals treated with β-L-FTC and L-FMAU. This method also reduced covalently closed circular DNA (cccDNA) by 24 to 47%, compared to an increase of 64%-77% of cccDNA in untreated animals. cccDNA serves as a template for viral transcript synthesis by host RNA polymerase II. The claimed method can be used to treat HBV infections while avoiding the emergence of drug resistant strains and allowing long-term treatment that could deplete the residual pools of cccDNA.

The specification provides ample evidence to support that the claimed method is a potent combination therapy regimen for treating HBV infections and that this particular combination of agents offers several unexpected advantages for the treatment of HBV infections. These advantages were not disclosed or suggested by Schinazi, alone or in combination with Thyagarajan.

Schinazi describes sixteen genuses of compounds for use in treating HIV and HBV infections and that these compounds may be used in combination with a second antiviral agent (see col. 3-6.) Schinazi provides data pertaining to the HBV activity of six compounds, including β-L-FTC. Schinazi does not provide data on any combination therapy involving β-L-FTC or L-FMAU. Schinazi does not disclose or suggest that the particular combination of β-L-FTC, L-FMAU and interferon could be used to minimize viral rebound or to avoid the emergence of drug resistant strains of HBV.

Thyagarajan describes pharmaceutical compositions comprising plant-derived *Phyllanthus amarus* for the treatment of HBV, HCV and related viral infections. The Examiner refers to a list of agents in the background section of Thyagarajan. Thyagarajan notes that these agents, including several nucleoside compounds, have been studied for the treatment of HBV infection and that except for interferons, Lamuvidine and Phyllanthus amarus, "the others seem to be far from successful." Thyagarajan does disclose or suggest the claimed method. There is no motivation from the disclosure of Thyagarajan to combine β-L-FTC, L-FMAU and interferon in a method for treating HBV infections.

As previously discussed, Schinazi and Thyagarajan do not provide any motivation to one of ordinary skill in the art to specifically combine β-L-FTC, L-FMAU and interferon for administration together from among the large number of possible active agents described therein. The Examiner's suggestion that one can simply administer three pharmaceutically active compounds and have a reasonable expectation that the combination would be successful ignores the fact that the drugs may be inactive, antagonistic or cause new side effects if combined. As discussed in the specification on page 8, at the time of the present application, it was "still not known which combinations are effective to optimally substantially reduce or eliminate the human hepatitis B viral load in the host" and that in some instances, additional therapies "can actually be detrimental to the patient's well being." Applicants have previously provided scientific literature to support that even more recently success in combining even two anti-HBV agents "remains elusive" (see page 1033, left column, lines 36-37 of Osborn, "Antiviral options for the treatment of chronic hepatitis B," *Journal of Antimicrobial Chemotherapy*, vol. 57, p. 1030-1034, April 4, 2006). In this passage, Osborn cites an example of antagonism occurring with combination therapy including two nucleoside compounds, telbivudine and lamivudine. The selection of antiviral agents for combination therapy of HBV infections is not a trivial matter. Applicants submit that it would not have been obvious for one of skill in the art to employ β-L-FTC, L-FMAU and interferon in combination in a methods of treating HBV infections with improvements in viral rebound and drug resistance. Rather, the Examiner can only arrive at the specifically claimed three components through improper hindsight reconstruction.

In sum, there is no direction in the cited references to use β-L-FTC, L-FMAU and interferon in combination to treat HBV infections. One of skill in the art would not have been provided with an expectation of success with respect to the claimed administration of three anti-HBV agents. Applicants have provided a specific combination of antiviral agents which has been shown to demonstrate remarkable and unpredictable effects in *in vivo* models of HBV infection. The advantages of the claimed method could not have been predicted by one of skill in the art. Applicants respectfully request withdrawal of this rejection.

Having distinguished the independent claim from the art of record, Applicants submit that the claims dependent therefrom are patentable for at least the same reasons. However,

Applicants reserve the right to separately address the patentability of those claims in the future should that become necessary.

CONCLUSION

Based on the foregoing amendments and remarks, Applicants respectfully request reconsideration and withdrawal of the rejection of claims and allowance of this application.

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for consideration of this Amendment, or credit any overpayment, to Deposit Account No. 11-0890.

Respectfully submitted,
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